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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,602	03/01/2002	Matthew Patricelli	063391-0302	7925

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EXAMINER	
COUNTS, GARY W	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,602	PATRICELLI, MATTHEW	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *1-20 and 33-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-32 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

The amendment filed November 24, 2004 is acknowledged and has been entered.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claims 21, 22, 24, 25, 27, 28 and 48 are rejected under 35 U.S.C. 102(e) as being anticipated by Cravatt et al (US 2002/0045194).

Cravatt et al disclose methods for detecting active proteins in samples (p. 14, para. 0128). Cravatt et al disclose the sample can be a proteome (p. 12). Cravatt et al disclose contacting the sample containing the active proteins with activity based probes (para. 0128). Cravatt et al disclose digesting the sample with a protease to create a mixture of peptides (para. 0128, lines 23, 24). Cravatt et al disclose isolating (separating) peptides covalently tagged with an activity based probe (para. 0128, lines 24-26). Cravatt et al disclose characterizing the tagged peptides by mass spectrometry and identifying the active proteins by mass spectrometry (para. 0128, lines 27-35). Cravatt et al disclose that the probe may contain a fluorescent moiety (p. 11, para. 0110).

With respect to the recitation "specifically binds predominantly to a single target site" as recited in the instant claims. Cravatt et al disclose that the activity based probes are comprised of the formula R*(F-L)-X (para 0083) and discloses a list of ligands X which are used in the formula (para. 0095). This activity based probe is the same as the activity based probe disclosed by applicant on page 15, paragraph 0049 of the specification and contains the same ligands (see pages 16-17, paragraph 0055 of the specification). Therefore, the activity based probe of Cravatt et al would inherently specifically bind predominantly to a single target site.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 21-28, 30-32 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (US 2002/0076739) in view of Cravatt et al (US 2002/0045194).

Aebersold et al disclose an isotope-coded affinity tag (chemical probe) for use in methods of determining target protein abundance between proteomes (complex protein mixtures). Aebersold et al discloses that these chemical probes bind to specific sites of target proteins (p. 2, paragraph 0017). Aebersold et al disclose contacting the complex protein mixture with the chemical probes (p. 7, col 1, lines 1-14). Aebersold et al disclose digesting the proteins in the sample mixture with proteolyzing agents (p. 7, paragraph 0070). Aebersold et al disclose separating the affinity tagged peptides by affinity isolation procedures (p. 7, paragraph 0071). Aebersold et al disclose analyzing the isolated-tagged peptides (those containing the probe) by liquid chromatography-mass spectrometry or capillary electrophoresis-mass spectrometry (p. 7, paragraph 0072). Aebersold et al disclose the removal of excess affinity tagged reagent (probe) prior to the step of digestion (p. 7, paragraph 0069). Aebersold et al disclose the use of internal standards in the method (p 6).

Aebersold et al differ from the instant invention in failing to teach the probe is an activity based probe.

Cravatt et al disclose probes that have specificity to the active form of proteins (abstract). Cravatt et al disclose that these probes provides for methods for the measurement of specific active proteins in a proteome (p. 12, paragraphs 0116-0018). Cravatt et al disclose that the probe may contain a fluorescent moiety (p. 11, para. 0110). Cravatt et al disclose the use of antibodies to capture ligands comprising a fluorescent moiety (p. 9, paragraph 0095). Cravatt et al disclose that these activity based probes provide for methods of measuring protein activity in proteomics, as

opposed to protein abundance (paragraph 0005). Cravatt et al disclose that active target proteins such as enzymes are key to almost every biologic process and that current preteomic approaches are limited to abundance of active target proteins and that this is a key limitation because the activity of enzymes is often regulated by post-translational modification (paragraph 0005).

It would have been obvious to one of ordinary skill in the art to substitute the activity based probe such as taught by Cravatt et al for the probe of Aebersold et al because Cravatt et al recognized the need for methods of measuring protein activity in proteomics, as opposed to protein abundance (taught by Aebersold et al). Further, Cravatt et al discloses that active target proteins such as enzymes are key to almost every biologic process and that current preteomic approaches are limited to abundance of active target proteins and that this is a key limitation because the activity of enzymes is often regulated by post-translational modification. Therefore, a skilled artisan can have a reasonable expectation of success in incorporating the activity based probes taught by Cravatt et al in the method of Aebersold et al.

6. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al and Cravatt et al in view of Little et al (US 2003/0003465).

See above for teachings of Aebersold et al and Cravatt et al.

Aebersold et al and Cravatt et al differ from the instant invention in failing to teach prior to the proteolyzing step, the one or more active target protein bound to the probe are bound to a solid support.

Little et al disclose immobilizing a target polypeptide (protein) to a solid support. Little et al disclose that the target polypeptide (protein) can be immobilized by a streptavidin or avidin to biotin interactions (p. 9, paragraph 073). Little et al disclose that the immobilization of a target polypeptide (protein) provides a means to isolate the polypeptide, as well as a means to manipulate the isolated target polypetide prior to mass spectrometry (p. 3, lines 1-6). Little et al disclose that the term polypeptide and protein are interchangeable (p. 5, paragraph 0045).

It would have been obvious to one of ordinary skill in the art to immobilize the active target protein complex of Aebersold and Cravatt et al to a solid support prior to the proteolysing step because Little et al teaches that the immobilization of a target polypeptide (protein) provides a means to isolate the polypeptide, as well as a means to manipulate the isolated target polypetide prior to mass spectrometry. Further, Aebersold et al teaches isolating the bound complex from excess probe prior to the proteolyzing step. Therefore a skilled artisan would have a reasonable expectation of success immobilizing the active target protein complex prior to a proteolyzing step.

Response to Arguments

7. Applicant's arguments filed November 24, 2004 have been fully considered but they are not persuasive.

Applicant argues that applicant's invention distinguishes over Cravatt et al. Applicant argues that Cravatt et al requires the use of sets of probes (e.g., a light probe and a heavy probe, see paragraph (0128) at page 14 of Cravatt) for the analysis contemplated therein. This is not found persuasive because it appears that applicant is

relying on the amendment to the claims in which a single activity based probe that specifically binds predominantly to a single target site on the one or more active target proteins is used. However, the comprising language as recited in the claims would include the inclusion of other components. Unless there is a recitation in the claims which excludes other components, the claims as recited encompasses the teachings of Cravatt et al.

Applicant argues that Aebersold does not disclose or suggest a method as recited in the instant claims. Applicant states that prior to the present invention, a standard belief in the mass spectrometry community for identification of proteins was that a single peptide could not give data with high enough confidence to unambiguously identify a protein through automated sequence searching algorithms. Applicant refers to references Florens L et al., Nature 419:520-526 and Adkins JN et al., Molecular and Cellular Proteomics 2002, December, pp.947 and Washburn MP et al., Nature Biotechnology, 2001, vol 19, pp 242-247 to support this statement. Applicant further argues that the probes of Aebersold increase the complexity of the sample and that a labeled sample according to Aebersold is digested, the number of labeled peptide species is substantially increased, typically at least 10X versus the number of labeled proteins. This is not found persuasive because the applicant is arguing the references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed.

Cir. 1986). Further, copies of the Florens et al., Adkins et al., and Washburn et al references which applicant refers to have not been provided and are not listed on an IDS and therefore, the relevance of the references cannot be determined (see also arguments based toward the following references in which applicant referred to but did not provide a copy of the references, Aebersold RA and Goodlet Dr, Chemical Reviews, 2001, vol 101, pp 269-295; Shen Y et al., Analytical Chemistry, 2004, 76, pp 1134-1144).

Applicant argues that Cravatt et al is unable to cure the deficiencies of Aebersold. Applicant further argues that no motivation has been provided to combine the cited references. Applicant states that it is only with improper hindsight analysis, having benefit of Applicant's specification that the asserted combination of references can be applied to the present claims. This is not found persuasive because the Examiner specifically disclosed the motivation to combine the two references because Cravatt et al recognized the need for methods of measuring protein activity in proteomics, as opposed to protein abundance (taught by Aebersold et al) and further because Cravatt et al discloses that active target proteins such as enzymes are key to almost every biologic process and that current proteomic approaches are limited to abundance of active target proteins and that this is a key limitation because the activity of enzymes is often regulated by post-translational modification. Therefore a skill artisan would have a reasonable expectation of success in incorporating the activity based probes taught by Cravatt et al in the method of Aebersold et al.

8. Applicant argues that Little is unable tot cure the deficiencies of the primary references Aebersold and Cravatt and that the asserted combination of references can only be advanced with improper hindsight analysis, having benefit of Applicant's specification. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary Counts
Examiner
Art Unit 1641
January 21, 2005

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1/24/05